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# The use of microcomputer-based psychomotor tests for the evaluation of benzodiazepine effects on human performance: a review with emphasis on temazepam

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1 The literature relating to the effects of benzodiazepines in general, and temazepam in particular, on human psychomotor performance as assessed using microcomputer-based testing batteries is surveyed.

2 The adverse effects of central nervous system depressants on performance is an important mediocolegal issue and frequently comes into question in on-the-road and on-the-job accidents. The use of microcomputer-based testing batteries allows for performance evaluation both in the laboratory and at-the-scene, as well as providing the opportunity to model a large number of different behaviours required in routine yet complex psychomotor tasks.

3 The conclusions in general are: (1) The benzodiazepines as a class of drugs impair both cognitive and motor performance. These effects are often subtle when low doses are involved or when testing occurs the morning following evening administration of the medication. (2) No single psychomotor task adequately simulates complex daily tasks such as automobile driving. A battery of tests that evaluates a number of the components of such tasks is necessary to determine adequately the full range of effects of these medications.

**Keywords** benzodiazepines temazepam human psychomotor performance

## Introduction

Benzodiazepines are the most commonly prescribed medications for the short-term management of anxiety. Members of the 1,4-benzodiazepine class are also indicated for the relief of insomnia both secondary to and unrelated to anxiety. All members of this class of drugs cause sedation varying only in potency concerning this effect. Although the number of prescriptions for anxiolytic benzodiazepines has been decreasing, those benzodiazepines primarily indicated for insomnia show no such trend. The sedation associated with the appropriate and proper use of benzodiazepines is a valuable therapeutic effect. When sedation lasts into the following day or when these sedative-hypnotic drugs are inappropriately used sedation becomes an adverse side effect.

The relationship between a sedative-hypnotic and impaired performance of psychomotor tasks has been well documented with ethanol. Epidemiologic data and laboratory and field tests have shown that blood alcohol concentrations may correlate with performance impairment. The expectation that other sedative-hypnotics will also impair performance has generated a considerable amount of research. The benzodiazepines have been extensively studied to determine if psychomotor impairment is associated with their appropriate or inappropriate use. Impairment associated with the use of many of the benzodiazepines, especially diazepam, has been established in a number of studies. Less well established is impairment associated with temazepam use. Correlation between blood and/or urine levels of benzodiazepines and performance impairment has also not been well established.

Many studies evaluating the effects of a number of members of the class of 1,4-benzodiazepines on various aspects of human performance have been conducted. Most studies utilize a number of different tasks in an effort to evaluate benzodiazepine effects on various motor skills and cognitive function. The literature reviewed here is not comprehensive but is intended to be representative of the types commonly employed in a

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performance testing battery. Particular attention is paid to temazepam and only those studies are reviewed in detail.

Despite the reduction in the number of prescriptions for benzodiazepines since 1979 (Hallstrom, 1989) they are still the most commonly prescribed psychoactive compounds worldwide (Nazareth & King, 1989; Rees, 1984; Wolf *et al.*, 1989). Although studies indicate that the recreational use (use without a prescription) of these medications is small, the misuse of these drugs among patients with a present or past indication or with a valid prescription is significant (Cleary & McIntire, 1989; Griffiths & Sannerud 1987; Mellinger *et al.*, 1984; Woods *et al.*, 1988). Even though well defined patterns of abuse and populations of abusers have not been clearly defined the large volume of research conducted and number of publications involving benzodiazepines seems to provide some indication that there is concern over the use, misuse and abuse of these drugs. Further evidence of this concern is the regulation promulgated by the New York State Commissioner of Health seeking to control strictly the writing and filling of benzodiazepine prescriptions (Freishtat, 1988). Ellis & Carney (1988) suggested that benzodiazepine abuse is significant enough to warrant consideration of non-pharmacologic management of anxiety. Orzack *et al.* (1988) suggest that there exists a population of recreational sedative users that are not considered drug dependent but are experienced users of these drugs. Betts *et al.* (1972) and Stanley *et al.* (1987) stated that the effects of benzodiazepines on psychomotor performance are important because hypnotics are used not only by insomniacs but also by apparently healthy subjects before a stressful event. Griffiths & Wolf (1990) indicate that professionals working with drug abuse patients confirm the non-medical use of benzodiazepines for their psychotropic effects ('getting high') and that they are bought and sold illicitly. Household studies (Balter *et al.*, 1984; Dunbar *et al.*, 1989; Mellinger *et al.*, 1984) also indicate that most of the benzodiazepine use is short term in duration and occasional in occurrence (< 30 days/year, 1 or 2 days at a time) consequently there is no significant development of tolerance to the sedation or behavioural effects of these drugs in most patients.

The increasing concern over the misuse of both illicit and prescription drugs (especially benzodiazepines) by the public-at-large and by the health care community in particular signals the need for an increased understanding of how these drugs affect human behaviour. The increasing number of government and industry sponsored drug testing programs supports the conclusion that there is a growing public awareness of the potential problems associated with drug abuse and misuse. Employee drug testing programs and drug abuse rehabilitation programs routinely employ laboratories involved in urine testing for drugs of abuse to screen and monitor employees and patients. The screening techniques employed by these laboratories provide information concerning recent drug use but typically can offer no indication of impairment or degree of intoxication. Although data confirming drug use are important for patients involved in drug rehabilitation there exists a need to correlate urine (or serum) drug levels to performance impairment, especially when employees using prescription drugs are involved.

The observation that certain agents can affect behaviour probably occurred with the first consumption of ethanol. Pharmacologists and other scientists have used the occurrence and observation of certain well defined and often trained behaviours as a tool for measuring and evaluating drug action for many years (Cleary & McIntire, 1989). A performance test battery may be used to assess the subtle behavioural effects of pharmaceuticals and other chemical substances. Such a battery is considered to be essential in the field of behavioural toxicology since behaviour is one of the criteria for judging the safety of new chemicals as specified in the Toxic Substances Control Act of 1976 (Kennedy *et al.*, 1987, 1989). A number of studies have shown that hypnotic benzodiazepines cause an impairment of psychomotor function as measured by various performance test batteries in both acute and chronic administration. The use of different tests and types of tests, different methodologies, doses and dosing schemes make comparisons between studies difficult (Hindmarch, 1980; Stanley *et al.*, 1987; Witternborn, 1979). It is also difficult to develop a clear picture of the effects of a single benzodiazepine hynotic due to the often contradictory and inconclusive results of many of these studies. Kennedy *et al.* (1989) suggest that the lack of a standardized human performance assessment battery has probably delayed the recognition of the deleterious behavioural effects of some drugs.

The goal of most of the behavioural or performance research in relation to sedative-hypnotics is to determine if use of these drugs is related to a decreased ability to perform routine, complex psychomotor tasks. The most commonly used example of such a task is automobile driving. As the workplace becomes more technologically sophisticated the ability to maintain a high level of vigilance during repetitive and often monotonous tasks becomes more critical. Automobile driving and workplace vigilance are tasks that researchers often attempt to simulate in the laboratory (Ferslew *et al.*, 1982). To date the bulk of the work in this area has investigated the effects of ethanol on driving performance (Evans *et al.*, 1973; Eves & Lader, 1989; Forney *et al.*, 1964; Garriott & Latman, 1976; Hughes & Forney, 1964; Krueger, 1986; Manno *et al.*, 1970). Over the course of the last 50 years, a considerable body of laboratory and epidemiological data has been collected concerning the adverse effects of ethanol consumption on driving performance. As a result of this long period of study a correlation between blood alcohol concentration (BAC) and impairment has been established. This relationship has been translated from the realm of behavioural toxicology to the realm of the courts by the legislation of the 100 mg 100 $ml^{-1}$ (0.10% w/v) BAC legally defining 'driving while intoxicated' in many states within the United States.

It is important to establish performance/drug level relationships for other sedative-hypnotics as has been established for ethanol. Because hypnotic benzodiazepines are commonly prescribed to individuals who continue their normal daily activities and, based on the large number of prescriptions written, 65 million in 1981

(Griffiths & Sannerud, 1987), the behavioural effects of sedative-hypnotic benzodiazepines should be evaluated. Since ethanol is also commonly used there is a rationale for including an ethanol/benzodiazepine interaction in such a psychometric study (Erwin *et al.*, 1986; Garriott & Latman, 1976; Griffiths & Wolf, 1990; Lery *et al.*, 1982; Linnoila & Hakkinen, 1974; Linnoila & Mattila, 1973; Linnoila *et al.*, 1974, 1981, 1990). There is also some evidence that ethanol effects are mediated through the gamma amino butyric acid (GABA) system and for that reason studies of the benzodiazepine-ethanol interaction may provide useful information concerning the pharmacokinetic and clinical effects of such an interaction (Clausen *et al.*, 1990; Misak, 1990). Part of the daily routine for many of these benzodiazepine users is automobile driving and the use of these psychotropic agents by drivers is considered to be on the increase. Sedation or residual sedation when the drug is used on the previous night is likely to interfere with the performance of routine everyday tasks, especially motor vehicle operation (Breimer, 1979; Brookhuis *et al.*, 1990; Clayton, 1976; Hindmarch, 1979; Jansen *et al.*, 1986; Smiley & Moskowitz, 1986; Stevenson *et al.*, 1986; Volkerts & O'Hanlon, 1986; Wittenborn *et al.*, 1979). The implications of these facts become evident as the epidemiological data are reviewed and an increased accident rate is associated with the use of hypnotic benzodiazepines (Hindmarch, 1976a; Honkanen *et al.*, 1980; Moskowitz, 1984; Skegg *et al.*, 1979; Smiley & Moskowitz, 1986).

Benzodiazepines were first utilized for the treatment of anxiety. There are currently a large number of benzodiazepines used as anticonvulsants, muscle relaxants, anaesthetic adjuncts and in the treatment of insomnia. They are distinctive among sedative-hypnotics in their wide margin of safety between therapeutic and toxic doses. There are a large number of 1,4-benzodiazepines available in different dosage forms for these different indications. Most of the members of this class of drugs are similar in their effects and side effects, differing only in potency and pharmacokinetic profile. The most common side effect of these medications is sedation, an extension of their CNS depressant action. With increasing doses, sedation and ataxia may become severe and motor impairment becomes apparent. Learning and immediate memory also seem to be impaired by therapeutic doses of some benzodiazepines (Eves *et al.*, 1988; Eves & Lader, 1989; Greenblatt *et al.*, 1989; Hindmarch, 1986; Reitan *et al.*, 1986; Warot *et al.*, 1987; Wittenborn, 1979). There is little indication though, that well established higher mental faculties are impaired (Wittenborn, 1979).

Hindmarch (1986) stated that the tendency of the 1,4-benzodiazepines to cause sedation is reflected in a breakdown of steering, road positioning and reaction time skills both in laboratory tests and in actual on the road driving tests. Driving requires a continual state of alertness, and the sedation and hangover effects resulting from the use of sedatives can jeopardize the driver and others by diminishing the wakeful state of the driver (Laurell & Tornos, 1986). Koelega (1989), in his review of benzodiazepines and vigilance performance, indicates that the many studies performed to date show that different performance tests are differentially sensitive to different drugs with no apparent pattern. He also suggests that the monotonous nature of the vigilance task makes such a task more relevant to everyday life than do short tasks in which subject motivation may play a role. Selection of tasks that adequately simulate or represent real-life events (e.g. automobile driving) is considered by some to be the weak point in performance research (Hindmarch, 1986; Sanders, 1986). Since the selection of laboratory tests that divide the driving task into separate measurable components has not been adequately accomplished a multifaceted approach is typically used. This approach usually takes the form of a battery of psychomotor tests administered to a subject.

The studies reviewed here used a variety of different tests combined into a large number of different test batteries. Some of the tests shown to be sensitive to the performance impairing effects of benzodiazepines are discussed. Only placebo controlled studies are included in this review and the results of those studies are typically expressed *vs* placebo.

## Reaction time

These tests evaluate motor response by requiring the subject to press a button in response to a critical stimulus. Number correct and latency to respond are normally determined as a measure of task performance. Both simple and choice reaction time have been frequently used. Simple reaction time involves only a motor response, e.g. how rapidly the subject presses a button after stimulus presentation. In choice reaction time (CRT) the subject is presented with a single stimulus that is one of a number of alternatives. This test assesses sensorimotor performance by adding a recognition time component (stimulus processing time) to the motor movement aspect of the simple reaction time test. Variations on these tests include addition of an auditory stimulus preceding the visual stimulus (alerting reaction time test), use of only an auditory stimulus and no visual stimulus (auditory reaction time test), versions in which a button is released instead of a button pressed in response to a stimulus and many others. Frequently choice and simple reaction time tests are administered as part of the same battery. Simple reaction time is usually slowed by therapeutic doses of benzodiazepines when testing occurs within a few hours after administration of a single dose and that impairment typically diminishes after sleep (Chernik *et al.*, 1990; Erwin *et al.*, 1986; Johnson *et al.*, 1990; Judd *et al.*, 1990; Linnoila *et al.*, 1981; Moskowitz *et al.*, 1990; Patat *et al.*, 1988). When long half-life benzodiazepines are administered (e.g. diazepam) impairment may continue into the next day or for a number of days under a continuous dosing schedule (Eves & Lader, 1989) indicating that tolerance may not develop in some behaviours. However, as the period of continuous daily administration is lengthened, despite increased doses, these behaviours may become resistant to the impairing effects of the drug (Hoehn-Saric & McLeod, 1986; McLeod *et al.*, 1988). Choice

reaction time seems to be sensitive to the effects of benzodiazepines under the same types of conditions seen with simple reaction time tests. Those studies that evaluate the effects of a benzodiazepine within the time frame of the half-life of a therapeutic dose of the parent compound typically detect impairment with these tests (Nikaido & Ellinwood, 1987; Preston *et al.*, 1988; Roache & Griffiths, 1987; Seppala *et al.*, 1976; Subhan *et al.*, 1986; Warot *et al.*, 1987). In a study by Schaffler & Klausnitzer (1989) impairment was noted with a subchronic dose of bromazepam over a 7 day period but in a study by Preston *et al.* (1988) subtherapeutic doses of lorazepam did not impair choice reaction time performance. Although it may appear that the measures of reaction time tests (latency to respond and number of correct responses) are the same despite the variation of the test they probably measure different skills or at least different combinations of skills depending on the variations of the basic test. For example, in certain studies choice reaction time was not sensitive to the impairing effects of a benzodiazepine but simple reaction time was (Patat *et al.*, 1988; Seppala *et al.*, 1976), alerting simple reaction time was not affected but simple and choice reaction time were (Preston *et al.*, 1988) and auditory reaction time was impaired but simple and choice reaction time were not (Chernik *et al.*, 1990; Johnson *et al.*, 1990; Judd *et al.*, 1990; Moskowitz *et al.*, 1990; Sostmann *et al.*, 1989; Tazaki *et al.*, 1989). It is difficult to determine which of the many variants on reaction time testing are more sensitive to the subtle impairing effects of benzodiazepines because of the wide range of dosing and testing schedules utilized in these studies. It is important to realize that the results of such a variety of testing devices are probably not interchangeable between drugs or studies.

**Digit symbol substitution**

The digit symbol substitution test (DSST) from the Wechsler Adult Intelligence Test (Wechsler, 1981) like reaction time tests has been presented in a number of different forms. Although the presentation of the test may be different each version is, in essence, similar to the original paper-and-pencil test. The task requires sustained attention and concentration and evaluates response speed and recognition of sensory information. The test is one of visuo-motor coordination and therefore contains a motor aspect although the principal determinant of performance is the recording of visual information (Hindmarch, 1980). The number of substitutions whether digits substituted, squares filled, symbols substituted or patterns reproduced over a period of time (usually less than 3 min) is the normal measure in these tasks. Computerized versions of this test are among the most frequently used psychomotor tests in drug studies. The results reported with the DSST are highly variable between studies and drugs. The benzodiazepines in therapeutic hypnotic and anxiolytic doses generally result in a decrease in the DSST measure (digits substituted, etc.) over a 6 to 8 h period of time following administration (Eves & Lader, 1989; Gorenstein *et al.*, 1990; Jansen *et al.*, 1986; Kroboth *et al.*, 1988; Mattila *et al.*, 1986, 1988a,b; Nikaido & Ellinwood, 1987; Roache & Griffiths, 1987; Roache *et al.*, 1990; Smith & Kroboth, 1987; Sostmann *et al.*, 1989; Warot *et al.*, 1987; Wittenborn *et al.*, 1979). The impairment measured in these studies is long in duration for those benzodiazepines with longer half-lives although impairment does not seem to be directly associated with the half-life or with the presence of active metabolites with long half-lives. For example, Mattila *et al.* (1986) did not measure impairment on DSST, 3 h after a single 20 mg dose of diazepam (0.3 mg $kg^{-1}$, average subject weight $\approx$ 67 kg). Some studies, however, report conflicting results. Greenblatt *et al.* (1989) reported no impairment 1 h after 0.25 mg triazolam, but Sostmann *et al.* (1989) reported impairment over an 8 h period after the same dose, 10 mg diazepam decreased the number of substitutions up to 2 h after administration in a study by Jansen *et al.* (1986) but no impairment over a 24 h period in a study by Patat *et al.* (1988). Benzodiazepines are typically indicated for the short-term treatment of anxiety or insomnia and are frequently taken in the evening for a period of time that can range from a few days up to 4 months. A number of studies have evaluated the effects of consecutive evening administrations on performance the following morning. The majority of these studies show no impairment on the DSST on the morning following evening administration of hypnotic doses or after a number of consecutive nights of administration whether healthy or insomniac subjects were treated (Chernik *et al.*, 1990; Ellinwood *et al.*, 1990; Johnson *et al.*, 1990; Judd *et al.*, 1990; Mattila, 1988; Moskowitz *et al.*, 1990; Smith & Kroboth, 1987). Some interesting findings appear in these multiple day administration studies. Judd *et al.* (1990) reported no residual performance effects the morning following 1, 2, and 7 nights administration of 30 mg flurazepam, but did detect a decreased number of substitutions on the morning following the thirteenth and fourteenth nights administration. The accumulation of the active metabolite, desalkylflurazepam, may account for this late developing impairment. In a similar study, the accumulation of desmethyldiazepam (a long half-life active metabolite of diazepam), however, did not seem to alter performance after 6 weeks of daily treatment with 15 mg diazepam (Hoehn-Saric & McLeod, 1986; McLeod *et al.*, 1988). The development of tolerance to the behavioural effects of both the parent drug and metabolite over the long duration of these studies may account for the lack of impairment. The evaluation of benzodiazepine induced impairment over a short period of hours after drug administration is much more consistent between studies than the results seen with reaction time tests, despite the wide variety of symbol substitution tests employed. Results seem to correlate well between different studies based on dose equivalents of the drugs administered. Beyond a 6 to 8 h time period and in studies using consecutive nights of administration the results become much more difficult to interpret between studies even if the same dose of the same drug is administered. The digit symbol substitution test in general is a sensitive measure of the type of psychomotor impairing effects induced by benzodiazepines in a narrow time frame after administration.

**Critical flicker fusion threshold**

In this task subjects look at a flashing light and are required to discriminate flicker. The point at which the light appears to be continuous is termed the threshold and provides a measure of overall CNS arousal and activity. Specifically, it measures the subjects ability to distinguish discrete units of sensory data (Subhan *et al.*, 1986). The CFFT has not been used as extensively in benzodiazepine studies as the computerized versions of pencil-and-paper tests (e.g. DSST) and reaction time tests have. However, this test has been shown to be sensitive to the CNS depressant effects of a number of benzodiazepines. The majority of studies reviewed reported a decrease in flicker fusion threshold within a 5 to 8 h period after administration of a single hypnotic dose indicating depressed CNS activity within that time frame (Gorenstein *et al.*, 1990; Mattila *et al.*, 1988a, Patat *et al.*, 1988; Seppala *et al.*, 1976; Subhan *et al.*, 1986; Warot *et al.*, 1987). Many of these studies compared different benzodiazepines and reported similar levels and duration of impairment for equivalent doses of these drugs. Some conflicting results were reported, however, for a single 10 mg dose of diazepam. Jansen *et al.* (1986) reported no change in flicker fusion threshold at 1 and 2 h after administration, but other studies reported impairment with this dose at both 1 and 5 h after administration (Patat *et al.*, 1988; Seppala *et al.*, 1976). A decreased threshold was also noted for up to 3 h after waking in the morning following 1 and 7 consecutive nights administration of 15 mg diazepam (Mattila, 1988) and after 4 consecutive nights administration of 10 mg diazepam (Eves & Lader, 1989). The CFFT appears to be sensitive to the residual effects of a benzodiazepine with a long half-life ($t_{1/2}$ = 20–80 h) and an active metabolite with a long half-life (desmethyldiazepam, $t_{1/2}$ > 20 h) because a single 5 mg dose of nitrazepam ($t_{1/2}$ = 28 h, no active metabolites) did not impair performance on the morning following administration (Hindmarch, 1979). The development of tolerance to the threshold decreasing effect of benzodiazepines seems to develop fairly rapidly with those drugs having short to intermediate action ($t_{1/2}$ < 20 h). Warot *et al.* (1987) measured a decrease in flicker fusion threshold at 1 h after 0.25 mg triazolam but not at 6 h. Both 2 mg lorazepam and 0.5 mg alprazolam decreased threshold 1 h after a single dose but not after 3 doses in a single day (Subhan *et al.*, 1986). This tolerance may account for the lack of residual nitrazepam effects despite the fact that testing occurred well within a single half-life of the drug. The next day impairing effects associated with diazepam use may then be attributable to the presence of an active metabolite. The formation of such metabolites must then be a consideration in the evaluation of any benzodiazepine's effect on performance. An interesting variation on the CFFT was employed by Sostmann *et al.* (1989). In these studies the measure was when flicker was detected in a light whose sinusoidal fluctuation was initially set at a level at which a steady light was perceived instead of measuring when a flickering light appeared steady. Using this variation decreased CNS activity was measured over an 8 h period for 0.25 mg triazolam in contrast to the 2 h period of observed impairment on the more traditional version of the test (Warot *et al.*, 1987). The CFFT appears to be quite sensitive to the CNS depression associated with the use of benzodiazepines and can readily be incorporated into a computer-based testing battery.

**Tapping rate**

This test samples motor ability and typically involves striking a key or alternate keys on a keyboard as rapidly as possible over a short time period (e.g. 10 s). Inclusion of such a test in a battery allows for analyzing the motor component of reaction time and pursuit tracking tasks that may also be included in that battery. Those studies reviewed that included tapping rate have reported that doses of drugs that did not affect more complex behaviours (e.g. reaction time, tracking, etc.) also did not impair tapping rate. As doses of these drugs were increased the complex behaviours were affected while tapping rate remained unaffected. These results indicate that the impairment measured in those studies was not simply a function of the subject's inability to perform the test because of loss of muscle control or some pure motor effect. Eventually doses were reached at which tapping rate was also impaired (Eves & Lader, 1989; Leigh *et al.*, 1991; Mattila, 1988; Mattila *et al.*, 1986, 1988a; Patat *et al.*, 1988; Preston *et al.*, 1988).

**Tracking**

Tracking is a measure of visuo-motor coordination and may contain elements of reaction time, fine and course motor control and attention. The pursuit rotor is considered to be the most basic measure of visuo-motor performance (Hindmarch, 1980). Compensatory and adaptive tracking use the subject's input while attempting to maintain the position of an indicator on screen to move that indicator out of a defined range. The root mean square of the distance of the indicator from the center of the screen is usually the performance measurement in these tasks. Pursuit tracking requires the subject to follow a path generated by the device and superimpose their own path over that one. Sinusoidal patterns are commonly used and the performance measurement is usually the subjects deviation from the generated wave summed over the entire test pattern. Tracking tasks, like reaction time tests, evaluate skills that are affected by hypnotic doses of benzodiazepines only a short period of time after administration (Nikaido & Ellinwood, 1987; Linnoila *et al.*, 1990; Stoller *et al.*, 1976; Subhan *et al.*, 1976). In many studies a reduction in tracking ability was observed 2 to 4 h after drug administration but not the morning following either a single dose or a number of consecutive evenings administration of the same dose (Erwin *et al.*, 1986; Fisch *et al.*, 1990; Laurell & Tornros, 1986; Linnoila *et al.*, 1981; Mattila, 1988; Mattila *et al.*, 1988b; Nicholson, 1979, 1986). Smiley & Moskowitz (1986) however, reported that 10 mg diazepam impaired driving simulator performance after a single

morning dose and after 8 days of continuous dosing (10 mg in the morning and 5 mg at night) when testing occurred 1 h after the morning dose. The lack of measurable impairment in the morning following evening doses may be attributable either to a lack of residual impairment or insensitivity of the tests to the type of behavioural effects that linger after sleep and probably not the development of tolerance to the drugs affects on the skills evaluated by tracking tasks. Those studies testing next-day residual effects do not show differences between long and short acting benzodiazepines nor do they show differences between those benzodiazepines with active metabolites *vs* those with inactive metabolites. The results of the different variations on tracking (e.g. adaptive, compensatory, pursuit, etc.) among the studies reviewed tended to yield similar results for the same doses of the different benzodiazepines evaluated. This indicates that the subtle differences in types of tracking may be unimportant in a general evaluation of a drugs ability to impair automobile driving related skills. Although none of the tracking tasks discussed, including driving simulators, adequately reproduce the driving task in the controlled environment of the laboratory, they all model aspects of driving and are sensitive to the impairing effects of therapeutic doses of many benzodiazepines. This is especially true when testing occurs within a few hours after drug administration. Testing within this time frame models an abuse scenario in which individuals self-administer a hypnotic or anxiolytic drug and proceed about their normal daily activities. Tracking tasks used in these situations provide valuable information concerning the immediate effects of drugs on routine yet complex psychomotor tasks to the medicolegal community. The need to perform comparison studies between actual driving performance, driving simulator performance and tracking performance is critical, as is the need to correlate blood levels of psychoactive drugs to any associated performance decrement.

### Other tests

A number of other tests have been incorporated into computer-based test batteries or are suitable for adaptation into a computerized form. Those discussed here have not necessarily found wide application but may be useful additions to the tests most frequently used in performance studies. In the Stroop procedure a large disruption and delay occur in colour naming when a color is used to spell incongruent colour names (e.g. the word BROWN is written in red letters). The task measures visual selective attention and the ability to encode and appropriately respond to perceptual information (Dyer, 1973). That ability is disrupted and colour naming is delayed over a 3 h period after 2 mg lorazepam (Preston *et al.*, 1988). Divided attention tasks are frequent additions to tracking, reaction time and DSS tests in testing batteries. In divided attention tasks subjects are required to share attention between two or more simultaneous subtasks. Divided attention tasks are thought to be extremely sensitive to drug effects because they place subjects in an 'information overload' situation in which the capacity to absorb and respond to all relevant information is taxed (Moskowitz, 1984). Although nearly any two tasks can be combined, the information processing demands should be such that either one or both of the subtasks are performed at a lower performance level than would be the case if performed alone. A critical concern in the development of a divided attention test is that the combination of tasks must not overload the subject to the degree that one of the subtasks is neglected or ignored in an effort to perform the other. Combinations involving tracking tasks and some other subtask such as a reaction time test or vigilance task are the most frequently used. Divided attention tasks composed of these elements have been found to be sensitive to both acute and chronic (multiple nights) administration of benzodiazepines (Chernik *et al.*, 1990; Ellinwood *et al.*, 1990; Erwin *et al.*, 1986; Hoehn-Saric & McLeod, 1986; Johnson *et al.*, 1990; Judd *et al.*, 1990; Krueger, 1986; Linnoila *et al.*, 1981; Moskowitz *et al.*, 1990; Tornross & Laurell, 1990). The ability to share attention between two tasks is a requirement in many routine tasks, especially automobile driving, and so it is important to evaluate the effects of psychoactive drugs on this ability. The psychomotor impairing effects of benzodiazepines have also been noted on simple arithmetic tests, digit recall and matching-to-sample performance (Forrest & Galletly, 1988; Roache & Griffiths, 1987; Roache *et al.*, 1990). These tasks, as well as more commonly used tasks such as DSST are computer versions of paper-and-pencil tests. Many of those types of tests are suitable for adaptation to computer use but have not been utilized in that format. An example, the letter cancellation or deletion test (the subject deletes as many occurrences of a single letter from a text as possible) is commonly administered in a paper-and-pencil version. The number of letters cancelled was decreased by therapeutic doses of lorazepam, diazepam and triazolam from 1 to 3 h after administration (Forrest & Galletly, 1988; Gorenstein *et al.*, 1990; Mattila *et al.*, 1988a) but not by midazolam and lormetazepam on the morning following evening administration (Rettig *et al.*, 1990).

### Temazepam studies

A number of studies that used computer-based testing batteries to evalute the effects of temazepam on human psychomotor performance are reviewed below with a summary of those results in Table 1. Temazepam is available in two formulations, a hard gelatin capsule (the only formulation available in the U.S.) and as a solution in a soft gelatin capsule (available in Europe). Where the exact formulation used in a study was described that information is included.

*Hindmarch (1975)* Choice reaction time and critical flicker fusion threshold tests were administered in the morning following a single evening dose of 15, 20 or 30 mg temazepam. The 15 and 30 mg doses were administered as hard gelatin capsules and the 20 mg dose was

**Table 1** Summary of temazepam/performance studies

| *Dose (mg)* | *Test time (h after administration)* | *Subjects (number, status, sex)* | *Task* | *Measure* | *Result* | *Study* |
|---|---|---|---|---|---|---|
| 15<br>20<br>30 | morning after 1 night administration | 18 male<br>12 female subjects<br>(healthy) | CRT<br><br>CFF | # correct and latency to respond, frequency | 30 mg – impaired CRT and CFF, no impairment with other doses | Hindmarch (1975) |
| 10<br>20<br>30 | morning after 1, 2, 3, and 4 nights administration | 16 male<br>14 female subjects<br>(healthy) | CRT<br><br>CFF | # correct and latency to respond, frequency | 30 mg – impaired CRT, CFF all days, no impairment with other doses | Hindmarch (1976b) |
| 15<br>30 | morning after 1 night administration | 20 insomniacs | CRT<br><br>CFF | # correct and latency to respond, frequency | 30 mg – impaired CRT, CFF,<br>15 mg – no impairment | Hindmarch (1979) |
| 10<br>20<br>30 | morning 10–16 h after administration | healthy males | adaptive tracking | distance from target | impaired only at 0.5 h after morning administration of dose | Nicholson (1979) |
| 10<br>20 | 0.5–6.5 | | | | | |
| 15<br>30 | 3.5, 10, 22.5 h after 1 and 2 nights administration | 14 healthy male subjects | DSST, free recall, time estimation, reaction time, arithmetic, platform, symbol copying | multiple measures | 15 mg – no impairment<br>30 mg – DSST, platform, free recall impaired @ 3.5 h | Roth *et al.* (1979) |
| 20<br>40<br>60 | morning after 7 nights<br>20 mg (first 7 nights)<br>then 40 mg (7 nights)<br>then 60 mg (7 nights) | 4 male 14 female subjects with insomnia | CRT<br><br>CFF | # correct and latency to respond, frequency | no impairment with any dose | Carrington & Hindmarch (1980) |
| 20 | 0.5, 1, 1.5, 2, 3, 4, 6, 9 and 12 h after administration | 6 male subjects (healthy) | saccadic eye movements | peak saccadic velocity | lowered velocity between 0.5 and 6 h | Bittencourt *et al.* (1981) |
| 20 | 12 h after administration | 12 healthy female subjects | driving course tests – weaving test, gap acceptance test | # passable and nonpassable gaps attempted or rejected,<br># hits through passable gap | weaving – no impairment,<br>gap test – ↑ # gaps hit | Betts & Birtle (1982) |
| 20 | 1, 9 and 12 h after 1 and 6 nights administration | 8 healthy subjects | CRT, saccadic eye movements, CFF | # correct, latency to respond, change in eye movement, flicker frequency | CRT – no impairment<br>impaired @ 1 h night 6<br>CFF – no impairment | Griffiths *et al.* (1986) |
| 20 | morning after 1 and 7 nights administration | 32 outpatients with sleep disorders | real driving test on 26 kM course | optimization quotient (measure of information assimilation) | ↓ quotient | Schmidt *et al.* (1986) |
| 10 | morning after 1 and 7 nights administration | 6 male 6 female subjects (healthy) | CRT, DSST, time estimation, card sorting, digit span | multiple measures | no impairment on any test at any time | Stanley *et al.* (1987) |
| 15 | 0.5, 1, 2, 3, 4, 6 and 8 h after administration | 52 healthy males and females | DSST | # correct substitutions | no impairment at any time | Greenblatt *et al.* (1989) |
| 20 | 1, 2 and 3 h after administration | 5 male 7 female subjects (healthy) | Maddox Wing<br>DSST<br>letter cancellation | exophoria and esophoria<br># correct substitutions<br># correct deletions | impairment at all times on all tests (LC @ 3 h no impairment) | Tuomainen (1989) |

administered as both the soft and hard gelatin capsules. Healthy male (18) and female (12) subjects were tested. Based on the results of a sleep evaluation questionnaire (SEQ) 20 and 30 mg doses were considered effective hypnotics while the 15 mg dose was not. The 20 mg dose in the soft capsule was rated as a better hypnotic by subjects and subjects also reported feelings of hangover with that formulation but not after the hard gelatin capsule. Impairment was significant on both tasks for the 30 mg dose with no impairment associated with the 15 mg dose or the 20 mg doses whether administered as the hard or soft capsule.

*Hindmarch (1976b)* CRT and CFF were used to evaluate the performance effects on the morning following 1, 2, 3 and 4 consecutive evenings administration of either 10, 20 or 30 mg temazepam administered as a solution in a soft gelatin capsule. Healthy male (16) and female (14) subjects were tested. The sleep evaluation questionnaire indicated that 20 and 30 mg doses over 4 nights were effective hypnotics. CRT and CFF performance was impaired only by the 30 mg dose and impairment was significant on all testing days. No residual impairment was apparent when placebo was given over the next 6 nights and testing occurred the following morning.

*Hindmarch (1979)* CRT and CFF were used to evaluate the effects of a single 15 or 30 mg dose (hard gelatin capsule) on the morning following evening administration in 20 patients suffering from insomnia. The 30 mg dose impaired CRT and CFF performance, but the 15 mg dose did not. A single 20 mg soft capsule also showed no impairment on these measures under the same dosing and testing conditions.

*Nicholson (1979)* An adaptive tracking task was used in this study to evaluate the effects of overnight administration of 10, 20 and 30 mg temazepam and morning administration of 10 and 20 mg temazepam. Healthy male subjects were tested and performance was observed from 10–16 h after overnight administration and from 0.5–6.5 h after morning ingestion. Tracking performance was not impaired after overnight use of any dose of temazepam although there was a non-significant trend toward impairment with the 30 mg dose. After morning administration performance was impaired at 0.5 h after ingestion of a 20 mg dose and no impairment was noted at any other time with either the 10 or 20 mg dose.

*Roth* et al. *(1979)* This study used a number of cognitive and psychomotor tests to evaluate the effects of 15 and 30 mg temazepam ingested 30 min before bedtime on 2 consecutive nights at 3.5, 10 and 22.5 h after drug administration. Only the results of the psychomotor tests will be reported here. Fourteen (14) healthy males were used as subjects. The Stanford Sleepiness Scale and the Bond Sleep Self-Rating Scale were used to evaluate the effectiveness of each dose as an hypnotic. The 15 mg dose was not considered an effective hypnotic and it did not impair performance as measured by any of the tests. The 30 mg dose was considered to be an effective hypnotic and impairment was significant at 3.5 h on DSST and a platform stability test; reaction time was not impaired at this dose.

*Carrington & Hindmarch (1980)* CRT and CFF were used to measure the performance effects associated with three doses of temazepam over 3 weeks of continuous administration. Fourteen (14) female and four male patients suffering with insomnia were given evening doses of drug and tested in the morning according to the following scheme: 7 consecutive evenings with 20 mg and testing on the morning of the eighth day, followed by 7 nights with 40 mg and testing on the morning of the eighth day and concluding with 7 nights with 60 mg temazepam and testing on the morning of the eighth day. Results of the SEQ indicated that all doses were effective hypnotics, but varied from the results seen with healthy subjects in that no hangover effects were felt in the morning following the 40 and 60 mg doses. Performance effects as measured by the CRT and CFF tests were also at variance with results seen in healthy subjects in that no impairment was caused by any of the doses administered to patients with sleep disorders (other studies have shown impairment associated with 30 mg temazepam on the morning following evening administration in healthy subjects).

*Bittencourt* et al. *(1981)* Peak velocity of saccadic eye movements were quantitated and compared with serum concentration at 0.5, 1, 1.5, 2, 3, 4, 6, 9 and 12 h after 20 mg temazepam, 10 mg diazepam, 15 mg flurazepam, 5 mg nitrazepam or 10 mg desmethyldiazepam. Saccades are used to move the eye quickly from one point of focus to another (e.g. changing focus from a traffic light to a moving pedestrian). The peak saccadic velocity is a neurophysiological measure that may be used to evaluate the function of a pontine premotor pathway. Six healthy male subjects were tested. Subjective analogue scales showed a significant increase in 'sleepiness' after all active treatments which was greatest between 0.5 and 3 h. A significant increase in the 'clumsiness' rating occurred after temazepam, diazepam, nitrazepam and desmethyldiazepam which was most pronounced between 0.5 and 3 h. Saccadic duration was increased and peak saccadic velocity was lowered after all five treatments indicating altered function of the neurones in the pontine reticular formation and suggestive of impaired motor function. Significant lowering of peak saccadic velocity occurred at 0.5 h after temazepam and diazepam with the lowest values (i.e. greatest impairment) between 1.5 and 2 h and no impairment after 9 h. A significant negative linear correlation was observed between decreasing peak saccadic velocity and increasing serum temazepam, diazepam and nitrazepam concentration indicating that performance worsened significantly as serum concentration of benzodiazepines increased.

*Betts & Birtle (1982)* Two driving tests conducted on a road course were used to evaluate the effects of 20 mg temazepam (soft capsule) on the day following administration. The study used 12 healthy female subjects and tests were conducted 12 h post-drug. The first test was a weaving test in which the subjects drove as fast as possible over the course while weaving between plastic

cones; performance measures were time to complete the test and the number of cones hit. Temazepam did not affect performance on this test when compared with placebo scores. The second test was a gap acceptance test. Subjects drove 10 times around a circular course and at some point in the course were presented with a gap formed by two cones. The distance between the cones varied with every transit of the course. At a distance of 30 m from the gap subjects had to decide if the gap was passable (wider than the car) or non-passable (too narrow for the car to pass through). Performance measures were the time to complete the test, the number of passable and non-passable gaps attempted (those the subject tried to drive through) or rejected (those the subject drove around) and the number of passable gaps that were hit while attempting to drive through. After receiving temazepam the number of passable gaps hit was increased, but the time to complete the course and the ability to recognise passable gaps did not differ from placebo. The authors stated that these results suggested carelessness rather than increased risk taking resulting from drug use.

*Griffiths* et al. *(1986)* CRT, CFF and saccadic eye movements were measured in eight healthy subjects at 1 (23.00 h), 9 (07.00 h) and 12 (10.00 h) h after 1 and 6 consecutive nights of 20 mg temazepam. The saccadic eye movement task required the subject to follow the movements of a target presented on a monitor. The subjects' eye movements were monitored by recording an electrooculogram. The performance measure was the difference between eye movements while tracking after placebo and after temazepam administration. Peak saccade velocity is a rapid and sensitive marker of drug induced sedation and stimulation. Saccadic eye movements were impaired 1 h after ingestion on the sixth night but not at any other time or at any time after only a single days administration. No significant impairment was noted on the CFFT or CRT at any time on either day of testing.

*Schmidt* et al. *(1986)* This study also used a real driving test to evaluate the effects of 20 mg temazepam on the morning following drug administration. Temazepam was given every night for 7 consecutive nights to 32 outpatients with a history of sleep disorders and driving performance was tested on the morning following 1 and 7 nights of drug treatment. The driving test was conducted on a 25 km course including a 1 km straight section at the end of the course which the subject was to attempt to drive at a constant speed of 80 km $h^{-1}$. The total test time was approximately 1 h. Parameters measured during the test were steering angular velocity, driving speed, forward acceleration and diagonal acceleration. The authors transformed the data to provide a measure of driver control behaviour. The optimization quotient was calculated by dividing the steering angular velocity by the product of the forward acceleration and the diagonal acceleration. This quotient may be considered a measure of the information assimilation capacity of the driver. As the driver becomes less concerned with steering the optimization quotient decreases and the more effectively the driver assimilates information. Driving performance as measured by the optimization quotient improved *vs* predrug scores and also compared with 2 mg flunitrazepam on both driving days. This indicates that driving performance was qualitatively improved in subjects with sleep disorders on the morning following evening administration of 20 mg temazepam. The authors concluded that psychotropic drugs may improve performance in patients with certain medical and psychiatric disorders.

*Stanley* et al. *(1987)* Healthy male (6) and female (6) subjects were used in this study to determine the effects of 10 mg temazepam on psychomotor performance on the day following 1 and 7 consecutive nights of treatment. CRT, DSST, time estimation and simple and complex card sorting tests were given. Time estimation required subjects to estimate the passing of 30 s and the difference from actual elapsed time was the error measurement. In simple and complex card sorting subjects sorted a deck of 52 playing cards into two piles sorting by suit (one suit for simple and two suits for complex sorting) and the performance measure was time to sort. There was no significant difference between temazepam and placebo scores on any test on either day of testing.

*Greenblatt* et al. *(1989)* DSST performance was measured in 52 healthy male and female subjects 0.5, 1, 2, 3, 4, 6 and 8 h after a 15 mg dose of temazepam (hard gelatin capsule). Subjects indicated that the 15 mg dose was an effective hypnotic. Scores on the DSST did not significantly differ from placebo at any of the testing times.

*Tuomainen (1989)* This study compared two formulations of temazepam (soft gelatin capsule and uncoated tablet) in 20 mg doses on pharmacokinetic and pharmacodynamic aspects of the drug. Performance effects were evaluated by DSST, a letter cancellation task and Maddox wing test for heterophoria. In the letter cancellation test the subject must cancel out all occurrences of a given letter in a text. This test is similar to the DSST in that it evaluates recognition of sensory information and ability to concentrate. The Maddox wing test measures the balance of extraocular muscles and reveals exophoria and esophoria expressed in diopters. The test is considered to reflect alterations in motor skills performance. Healthy subjects (five male and seven female) received 20 mg temazepam and were tested 1, 2 and 3 h after drug administration. Both the gelatin capsule and the tablet formulations impaired performance on all of the tests at all testing times except that letter cancellation performance was not impaired after 3 h. This study also correlated plasma temazepam levels with performance for each test. The correlation between concentration as determined by a radioimmunoassay technique and performance on the DSST was significant ($r = -0.453$) as was the correlation between concentration and the increased exophoria measured by the Maddox wing test ($r = 0.234$). A significant concentration/performance correlation was not established for letter cancellation performance.

## Discussion

The studies reviewed here concerning temazepam effects on human psychomotor performance used a number of different tests and a number of variations of the same test. The results of many of these studies show either impairment or a trend toward impairment that is not statistically significant associated with the use of therapeutic doses of temazepam (15–30 mg). These studies, however, evaluated performance using only two or three short duration psychomotor and cognitive tests a single time on the morning following either one night or multiple nights use of the medication. Those studies that evaluated performance over a longer period of time after dosing showed continued impairment with 30 mg of temazepam while no impairment was seen with 15 and 20 mg doses. These studies seem to indicate that the impairment associated with the use of therapeutic doses of temazepam occurs within the first few hours after administration in healthy subjects on only some tests. The availability of different formulations of temazepam seems to have no significant effect on the performance effects associated with the drug's use. The peak plasma level is slightly, but not significantly, higher and the time to peak plasma level is shorter for the soft gelatin capsule than for either the hard gelatin capsule or for tablets (Fuccella, 1979; Tuomainen, 1989). However, elimination half-life and area under the curve calculations were the same for all formulations. The only apparent difference recorded in the above performance studies is the perceived hangover in subjects receiving the hard gelatin formulation compared to the soft capsule (Hindmarch, 1975). Residual effects on performance measured in that study were less for the soft capsule dose than for the hard capsule dose, but neither yielded effects significantly different from placebo. It is unclear whether the tests that do not indicate impairment are simply not sensitive to temazepam induced impairment at the doses tested or if temazepam simply does not impair the types or aspects of performance measured by those tasks. In those studies evaluating overnight performance the lack of formation of an active metabolite must certainly be considered as a probable cause for the lack of residual effects. Subjects with sleep disorders and healthy subjects as well appear to suffer adverse effects on the morning following evening administration only at doses of 30 mg or greater.

The general review of studies evaluating benzodiazepine performance on computer-based tests included a number of different benzodiazepines at different dosages in a number of different dosing and testing schedules. The large number of psychomotor tests and the even larger number of variations on standard tests such as tracking and reaction time provide and extensive amount of data concerning the behavioural effects of benzodiazepines. The variations in testing devices, testing and dosing schedules and the often conflicting results between studies makes it difficult to formulate a coherent picture concerning the effects of these drugs on psychomotor performance. This indicates that the performance impairing effects of therapeutic doses of benzodiazepines are subtle and not measurable by all types of psychomotor tests. The ability to detect and quantitate performance altering effects may be related to the dosing and testing schedules used, as well as, the insensitivity of the test. Another problem associated with the use of many of the tests described in this manuscript is the lack of information presented concerning validation of the test. It is unclear if many of these tests are simply accepted as valid based on their long and frequent use or if they have never been subjected to a rigorous validation procedure. The adaptation of pencil-and-paper test to microcomputer use requires a validation procedure even if the original tool has been shown to be valid. The authors are concerned that the importance of these validation procedures is frequently overlooked. This may mean that performance altering effects of a drug are not apparent simply because the test used did not provide a valid measure of performance. There is sufficient data, however, to indicate that cognitive and motor effects are associated with the use of many benzodiazepines. The extrapolation from those effects measured by laboratory tests to the ability to perform on-the-job or on-the-road is often difficult. It is clear that few researchers rely on a single test for evaluating drug effects but prefer a battery of tests in an effort to evaluate a number of different skills. This approach allows for the evaluation of a large number of performance measures and also an evaluation of how drugs affect different aspects of those behaviours (e.g. tapping rate tests are effective in evaluating the motor component of tasks that involve both motor and cognitive aspects). The types of tests that may be included in a testing battery are many and varied but the most commonly applied tests are compensatory tracking, DSST and simple and choice reaction time tests. Despite the wide use of these tests the use of a rigorously evaluated battery of stable and reproducible tests that evaluate cognitive, reactive, vigilance and risk-taking behaviours would make the interpretation of results simpler and more meaningful. It is also clear from this literature that such a battery of tests should be constructed in an effort to model the driving task and other routine yet complex psychomotor tasks. As the relationship between psychotropic drug use and automobile accidents and impaired job performance becomes more apparent (and more firmly established by means of epidemiological data) the need for standardized batteries of performance tests to evaluate the skills required in those tasks will also become more apparent.

To date, a strong correlation between the impairment or trend towards impairment indicated in these studies and the level of drug or metabolites in body fluids has not been established for temazepam or other benzodiazepines (Ellinwood *et al.*, 1990; Greenblatt *et al.*, 1989; Griffiths *et al.*, 1986; Jansen *et al.*, 1986; Johnson *et al.*, 1990; Kuitunen *et al.*, 1990; Linnoila *et al.*, 1990; Mattila *et al.*, 1986; Seppala *et al.*, 1976; Tuomainen, 1989). Many of the studies that analyzed drug and metabolite levels in plasma did not attempt to correlate those levels to performance effects. The majority of the studies mentioned above involve an analysis of impairment on the morning following use of the hypnotic medication since that is the typical use pattern. Evaluation of the effects of temazepam in a situation

where use simulates an abuse or misuse pattern (e.g. using the drug before and on the same day as some stressful event) will provide data of interest to the forensic drug testing community. Such a scenario will also provide a more suitable opportunity to obtain blood and/or urine levels of the parent drug and metabolites to establish a temporal relationship between performance and drug level. As benzodiazepines and other psychotropic drugs become more popular as recreational drugs and as abuse of these drugs becomes more apparent, establishing a correlation between blood levels and impairment (as has been done with ethanol) become increasingly important and necessary.

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